

[Chem. Pharm. Bull.]
33(1) 84-89 (1985)

Stereoselective Reduction of (*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one by Means of 1,4-Asymmetric Induction: Synthesis of Chiral 2-Amino-1-phenylethanols

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(Received May 1, 1984)

Stereoselective reductions of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) with several complex metal hydrides gave 2-4'-isopropyl-2'-oxo-1',3'-oxazolidinyl-1-phenylethanol (**3**) and 2-*N*-1'-isopropyl-2'-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**) in good yields. These products were diastereomeric mixtures and the diastereomer ratios were estimated to be *ca.* 75:25. The asymmetric 2-amino-1-phenylethanols (major products of **3** and **4**) were easily isolated by recrystallization. The absolute configuration of (1*S*,4'*S*)-**3** was determined by X-ray analysis.

The reductions of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) with complex metal hydrides gave 2-4'-isopropyl-1',3'-oxazolidinyl-1-phenylethanol (**7**) and **4** as diastereomeric mixtures (*ca.* 70:30).

Keywords—1,4-asymmetric induction; chiral phenacylamine; chiral phenylethanolamine; 1,3-oxazolidine chiral; 1,3-oxazolidin-2-one; stereoselective reduction; (*S*)-valinol

Chiral heterocyclic compounds can offer high stereoselectivity in their reactions,¹⁾ and we have reported the reactions of chiral (2*S*,4*S*)-2-aryl-4-isopropyl-1,3-oxazolidines, which are easily prepared from (*S*)-valinol and arylaldehydes.²⁾ Evans *et al.* have proposed that an extremely highly stereoselective 1,4-asymmetric induction occurs at the carbon atom adjacent to the acyl group in (*S*)-3-acyl-4-isopropyl-1,3-oxazolidin-2-ones.³⁾ In this work, we deal with the stereoselective reduction of (*S*)-4-isopropyl-1,3-oxazolidin-2-one having a phenacyl group at the 3-position by means of 1,4-asymmetric induction. Recently, syntheses of chiral 2-amino-1-phenylethanols from phenacylamines have become increasingly important in the

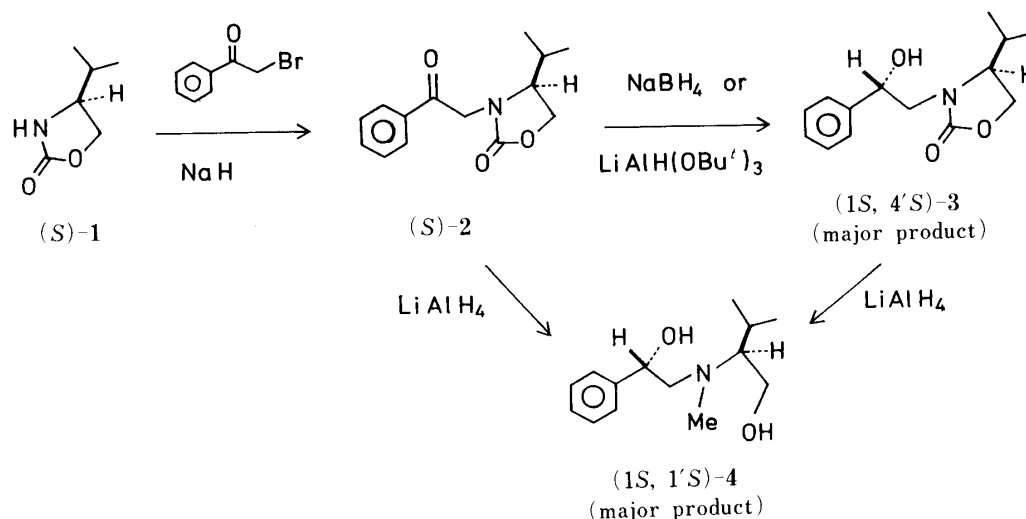


Chart 1

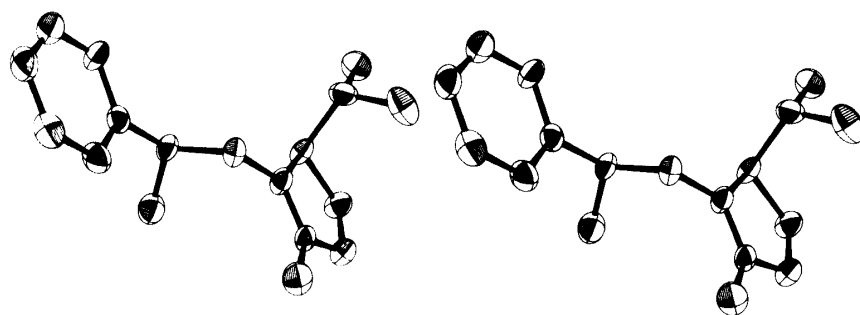


Fig. 1. Stereoscopic Drawings of the Structure of (1*S*,4'*S*)-3

design of medicinal agents.⁴⁾

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) was obtained by condensation of the sodium salt of 4-isopropyl-1,3-oxazolidin-2-one (**1**)⁵⁾ with phenacyl bromide. The signals of the methylene protons of the phenacyl group of this compound were observed at δ 4.32 and 5.08 ($J = 18.1$ Hz) in the proton nuclear magnetic resonance (¹H-NMR) spectrum, indicating that the molecule is fixed in a favorable conformation. The structure of this compound was confirmed by mass, infrared (IR), and ¹H-NMR spectroscopies.

The carbonyl bond of the phenacyl group was reduced with sodium borohydride and lithium tri-*tert*-butoxyaluminium hydride to give 2-4'-isopropyl-2'-oxo-1',3'-oxazolidinyl-1-phenylethanol (**3**) in 96 and 94% yields, respectively. These products were confirmed to consist of two diastereomers by observation of the ¹H-NMR spectra, in ratios of 83:17 and 71:29, respectively. The major product was isolated from the mixture of isomers by recrystallization to give colorless needles. Moreover, a single-crystal X-ray analysis of this compound established the configuration of the newly created asymmetric carbon atom at the 1-position; stereoscopic drawings of the molecular structure are shown in Fig. 1. Consequently, the absolute configuration of the major product obtained by the reduction of (*S*)-**2** was defined unequivocally to be (1*S*,4'*S*).

The reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) with lithium aluminium hydride occurred at the two carbonyl bonds of the phenacyl group and the 1,3-oxazolidin-2-one to give 2-*N*-1'-isopropyl-2'-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**) in 71% yield. This product was confirmed to consist of two diastereomers in a ratio of 72:28. The major product was isolated from the mixture by recrystallization, and it was identical with (1*S*,1'*S*)-**4** obtained by the reduction of (1*S*,4'*S*)-**3** with lithium aluminium hydride. Consequently, the absolute configuration of this compound was correlated to the (1*S*,1'*S*)-family.

In order to investigate the effect of the chiral heterocyclic compounds in 1,4-asymmetric induction, the reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) lacking the carbonyl group at the 2-position of the ring was carried out with complex metal hydrides. This compound (**6**) was prepared by condensation of (*S*)-valinol with formaldehyde, followed by reaction with phenacyl bromide, and showed in the ¹H-NMR methylene proton signals similar to those of (*S*)-**2**.

The reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) with lithium tri-*tert*-butoxyaluminium hydride gave a diastereomeric mixture of 2-4'-isopropyl-1',3'-oxazolidinyl-1-phenylethanol (**7**) in a ratio of 61:39 as determined by ¹H-NMR spectroscopy. On the other hand, the reduction with lithium aluminium hydride gave 2-*N*-1'-isopropyl-2'-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**), and the ratio of diastereomers was estimated to be 75:25. The major product of **7** was converted to (1*S*,1'*S*)-**4** by reduction with lithium aluminium hydride, so that the absolute configuration of this compound was clearly

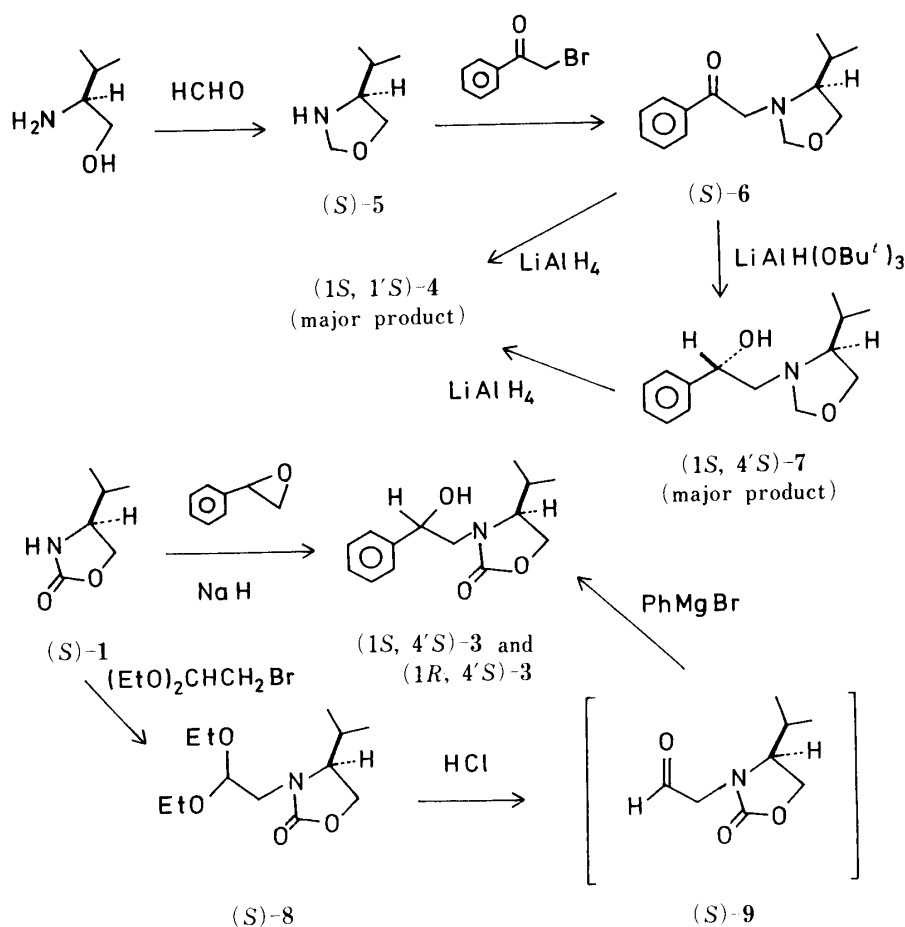


Chart 2

proved to be (1S,4'S).

We attempted to make use of the chirality of (S)-4-isopropyl-1,3-oxazolidin-2-one to synthesize the chiral 2-4'-isopropyl-2'-oxo-1',3'-oxazolidinyl-1-phenylethanol (3). The reaction of sodium (S)-4-isopropyl-1,3-oxazolidin-2-onate with 2-phenyloxirane⁶⁾ proceeded in low yield to give a mixture of (1S,4'S)-3 and (1R,4'S)-3 in nearly equal amounts. Next, (S)-3-2',2'-diethoxyethyl-1,3-oxazolidin-2-one (8) was prepared by condensation of (S)-1 with 2-bromo-1,1-diethoxyethane. Grignard reaction of 3-formylmethyl-1,3-oxazolidin-2-one (9), which was derived from 8, with phenylmagnesium bromide gave 3, but this reaction also proceeded to give nearly equal amounts of isomers.

The asymmetric reactions of 3-acyl-4-isopropyl-1,3-oxazolidin-2-ones were found to show extremely high stereoselectivity^{3,7)} due to the involvement of a chiral chelated intermediate⁸⁾ involving the acyl group at the 3-position of the 1,3-oxazolidine ring and the carbonyl group at the 2-position. The reduction of (S)-3-phenacyl-4-isopropyl-1,3-oxazolidin-2-one (2) with complex metal hydrides proceeded with 66–42% ds (diastereoselectivity),⁹⁾ and (S)-3-phenacyl-4-isopropyl-1,3-oxazolidine (6) gave the product with 50–22% ds in similar reductions. These results suggested that these reactions occur *via* a weak chiral chelate intermediate involving the phenacyl group and the 1,3-oxazolidine moiety.

Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer and the ¹H-NMR spectra were obtained with a JEOL JNM-FX100 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by

using the chemical ionization (CI, isobutane) method. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-180 polarimeter.

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one (2)—A solution of (*S*)-1 (2.06 g, 16 mmol) in toluene (50 ml) was slowly added, drop by drop, to a suspension of NaH (0.67 g, 28 mmol) in toluene (80 ml) with vigorous stirring, and the reaction mixture was refluxed for 9 h. A solution of phenacyl bromide (3.4 g, 17 mmol) in toluene (30 ml) was added dropwise to the suspension of the sodium 4-isopropyl-1,3-oxazolidin-2-onate. The reaction mixture was stirred at room temperature for 8 h, refluxed for 5 h, and then concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give (*S*)-2 as a colorless oil (2.13 g, 54%). IR (film): 1750 (C=O), 1700 (C=O) cm^{-1} . MS m/z : 248 ($\text{M} \cdot \text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.89 (3H, d, $J=6.8$ Hz, CHCH_3), 0.90 (3H, d, $J=6.8$ Hz, CHCH_3), 4.15 (1H, dd, $J=5.6$ and 7.8 Hz, OCH_2CH), 4.32 (1H, d, $J=18.1$ Hz, COCH_2), 4.40 (1H, t, $J=7.8$ Hz, OCH_2CH), 5.08 (1H, d, $J=18.1$ Hz, COCH_2).

(1*S*,4'*S*)-2-4'-Isopropyl-2'-oxo-1',3'-oxazolidinyl-1-phenylethanol (3)—(i) Reduction of (*S*)-2 with NaBH_4 : NaBH_4 (0.15 g, 4 mmol) was added little by little to a stirred solution of (*S*)-2 (0.49 g, 2 mmol) in methanol (5 ml), and the reaction mixture was stirred at -20 — -10 °C for 4 h. After addition of dilute acetic acid solution, the whole was extracted with ether and the ethereal solution was dried over anhydrous MgSO_4 . The removal of the solvent gave a mixture of (1*S*,4'*S*)-3 and (1*R*,4'*S*)-3 as a colorless crystalline solid (0.48 g, 96%). The product ratio was estimated to be 83:17 by $^1\text{H-NMR}$ spectroscopy.

The mixture of isomers was recrystallized from ether to give colorless needles of mp 90—91 °C. This compound was confirmed to consist of the major product, (1*S*,4'*S*)-3, by $^1\text{H-NMR}$ spectroscopy. IR (CDCl_3): 3450 (OH), 1740 (C=O) cm^{-1} . MS m/z : 250 ($\text{M} \cdot \text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.80 (3H, d, $J=6.8$ Hz, CHCH_3), 0.84 (3H, d, $J=6.8$ Hz, CHCH_3), 3.12 (1H, dd, $J=4.4$ and 14.4 Hz, NCH_2CH), 3.80 (1H, dd, $J=8.3$ and 14.4 Hz, NCH_2CH), 4.04 (1H, dd, $J=5.4$ and 9.0 Hz, OCH_2CH), 4.20 (1H, t, $J=9.0$ Hz, OCH_2CH), 4.93 (1H, dd, $J=4.4$ and 8.3 Hz, OCH_2CH_2). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.29; H, 7.75; N, 5.52. $[\alpha]_D^{20} +24.5^\circ$ ($c=4.0$, 95% ethanol).

The minor product of this reaction was (1*R*,4'*S*)-3; $^1\text{H-NMR}$ (CDCl_3) δ : 0.82 (3H, d, $J=6.8$ Hz, CHCH_3), 0.84 (3H, d, $J=6.8$ Hz, CHCH_3), 3.14 (1H, dd, $J=8.5$ and 14.6 Hz, NCH_2CH), 3.61 (1H, dd, $J=2.9$ and 14.6 Hz, NCH_2CH), 4.03 (1H, dd, $J=4.9$ and 8.6 Hz, OCH_2CH), 4.21 (1H, t, $J=8.6$ Hz, OCH_2CH), 4.98 (1H, dd, $J=2.9$ and 8.5 Hz, OCH_2CH_2).

(ii) Reduction of (*S*)-2 with $\text{LiAlH}(\text{OBu}')_3$: $\text{LiAlH}(\text{OBu}')_3$ (1.52 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-2 (0.49 g, 2 mmol) in THF (10 ml), and the reaction mixture was stirred at -20 — -10 °C for 9 h. After addition of ether (17 ml), the mixture was treated with a minimum quantity of H_2O , and the whole was dried over anhydrous MgSO_4 then concentrated under reduced pressure to give a mixture of (1*S*,4'*S*)-3 and (1*R*,4'*S*)-3 (0.47 g, 94%). The product ratio was estimated to be 71:29.

Crystallographic Measurements—A single crystal of (1*S*,4'*S*)-3 was grown in ether as a colorless column with dimensions of $0.2 \times 0.3 \times 0.5$ mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated $\text{MoK}\alpha$ radiation. The unit cell dimensions were determined by least-squares calculation with 20 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $3^\circ < 2\theta < 55^\circ$ with an average scan-rate of $4^\circ/\text{min}$. In total, 1848 independent reflections were collected, and 1015 satisfying the condition $F_0 < 2\sigma(F)$ were used for calculations.

Crystal Data— $\text{C}_{14}\text{H}_{19}\text{NO}_3$. $M=249.3$. Monoclinic. $a=10.494$ (3), $b=6.313$ (3), $c=10.438$ (4) Å, $U=683.2$ (5) Å³, $D_c=1.21$ g·cm⁻³, $Z=2$. $\mu(\text{MoK}\alpha)=0.8$ cm⁻¹. Space group $P2_1$.

Structure Analysis and Refinement—The structure was solved by the direct method using MULTAN¹⁰⁾ and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The R factor was finally reduced to 0.108.

(1*S*,1'*S*)-2-*N*-1'-Isopropyl-2'-hydroxyethyl-*N*-methylamino-1-phenylethanol (4)—Reduction of (*S*)-2 with LiAlH_4 : LiAlH_4 (0.23 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-2 (0.49 g, 2 mmol) in THF (7.5 ml) and the reaction mixture was stirred at -20 — -10 °C for 9 h. After addition of ether (10 ml), the mixture was treated with a small amount of H_2O . The solid was filtered off, and the filtrate was dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 –methanol (93:7) and a mixture of (1*S*,1'*S*)-4 and (1*R*,1'*S*)-4 was collected from all fractions. A colorless crystalline solid (0.34 g, 72%) was obtained. The ratio of the two isomers was estimated to be 72:28 by $^1\text{H-NMR}$ spectroscopy. Recrystallization of the mixture from *n*-pentane gave colorless plates of mp 60—61 °C; this product was confirmed to be the major one, (1*S*,1'*S*)-4, by $^1\text{H-NMR}$ spectroscopy. IR (CDCl_3): 3450 (OH) cm^{-1} . MS m/z : 238 ($\text{M} \cdot \text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (3H, d, $J=6.6$ Hz, CHCH_3), 1.00 (3H, d, $J=6.6$ Hz, CHCH_3), 2.47 (3H, s, NCH_3), 2.7—2.9 (2H, m, ABX Type, NCH_2CH), 3.42 (1H, dd, $J=9.0$ and 11.0 Hz, OCH_2CH), 3.66 (1H, dd, $J=4.6$ and 11.0 Hz, OCH_2CH), 4.75 (1H, dd, $J=5.4$ and 8.0 Hz, OCH_2CH_2). Anal. Calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.81; H, 9.96; N, 5.81. $[\alpha]_D^{20} +64.5^\circ$ ($c=4.0$, 95% ethanol).

The minor product of this reaction was (1*R*,1'*S*)-4; $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (3H, d, $J=6.6$ Hz, CHCH_3), 0.94

(3H, d, $J=6.6$ Hz, CHCH_3), 2.42 (3H, s, NCH_3), 2.72 (1H, dd, $J=9.5$ and 13.4 Hz, NCH_2CH), 3.00 (1H, dd, $J=3.7$ and 13.4 Hz, NCH_2CH), 3.38 (1H, dd, $J=9.5$ and 10.7 Hz, OCH_2CH), 3.69 (1H, dd, $J=4.6$ and 10.7 Hz, OCH_2CH), 4.75 (1H, dd, $J=3.7$ and 9.5 Hz, OCHCH_2).

Conversion of (1*S*,4'*S*)-3 into (1*S*,1'*S*)-4— LiAlH_4 (0.08 g, 2 mmol) was added, little by little, to a stirred solution of (1*S*,4'*S*)-3 (0.13 g, 0.5 mmol) in THF (3 ml), and the reaction mixture was stirred at -20 — -10°C for 4 h. After treatment with H_2O , the whole was extracted with ether. The ethereal solution was dried over anhydrous MgSO_4 and concentrated under reduced pressure to give (1*S*,1'*S*)-4 (0.08 g, 67%), which was identical with an authentic sample.

(*S*)-4-Isopropyl-1,3-oxazolidine (5)—Formaldehyde obtained by heating (180 — 190°C) of paraformaldehyde (2.7 g, 90 mmol) was bubbled into a stirred solution of (*S*)-valinol (6.18 g, 60 mmol) in ether (150 ml) on an ice-cold bath using nitrogen as a carrier gas, and the reaction mixture was stirred in the presence of MgSO_4 (14 g) for 1 h. After removal of the solid, the mixture was concentrated under reduced pressure and the residue was distilled *in vacuo* to give (*S*)-5 as a colorless oil, bp $85^\circ\text{C}/80$ mmHg, (2.86 g, 42%). IR (film): 3350 (NH) cm^{-1} . MS m/z : 116 ($\text{M}^+\cdot\text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (3H, d, $J=6.6$ Hz, CHCH_3), 1.06 (3H, d, $J=6.6$ Hz, CHCH_3), 1.9 (1H, s, NH), 2.91 (1H, q, $J=7.5$ Hz, CH_2CHCH), 3.22 (1H, t, $J=7.5$ Hz, OCH_2CH), 3.81 (1H, t, $J=7.5$ Hz, OCH_2CH), 4.32 (1H, d, $J=6.0$ Hz, OCH_2N), 4.53 (1H, d, $J=6.0$ Hz, OCH_2N).

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidine (6)—A solution of (*S*)-5 (0.58 g, 5 mmol) in THF (3 ml) was slowly added to a solution of phenacyl bromide (0.59 g, 3 mmol) and triethylamine (0.45 g) in THF (4 ml), and the reaction mixture was stirred on an ice-cold bath for 12 h. After removal of the solid, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give (*S*)-6 as a colorless oil (0.36 g, 52%). IR (CHCl_3): 1690 ($\text{C}=\text{O}$) cm^{-1} . MS m/z : 234 ($\text{M}^+\cdot\text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (3H, d, $J=6.6$ Hz, CHCH_3), 0.96 (3H, d, $J=6.6$ Hz, CHCH_3), 3.48 (1H, dd, $J=5.9$ and 8.5 Hz, OCH_2CH), 3.94 (1H, d, $J=16.6$ Hz, COCH_2N), 4.02 (1H, dd, $J=7.3$ and 8.5 Hz, OCH_2CH), 4.15 (1H, d, $J=16.6$ Hz, COCH_2N), 4.38 (1H, d, $J=5.9$ Hz, OCH_2N), 4.42 (1H, d, $J=5.9$ Hz, OCH_2N).

Reaction of (*S*)-6 with $\text{LiAlH}(\text{OBu}')_3$ — $\text{LiAlH}(\text{OBu}')_3$ (1.0 g, 4 mmol) was added, little by little, to a stirred solution of (*S*)-6 (0.47 g, 2 mmol) in THF (24 ml), and the reaction mixture was stirred at -20 — -10°C for 9 h. After addition of ether (10 ml), the mixture was treated with a minimum quantity of H_2O . The whole was dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 and a mixture of (1*S*,4'*S*)-7 and (1*R*,4'*S*)-7 was collected from all fractions. A colorless oil (0.24 g, 51%) was obtained. The product ratio was estimated to be 61:39 by $^1\text{H-NMR}$ spectroscopy. The mixture was rechromatographed on silica gel with CH_2Cl_2 to give (1*S*,4'*S*)-7 (major product) as the first fraction and (1*R*,4'*S*)-7 (minor product) as the second fraction. IR (film): 3500 (OH) cm^{-1} . MS m/z : 236 ($\text{M}^+\cdot\text{H}^+$). $^1\text{H-NMR}$ (CDCl_3) δ : (1*S*,4'*S*)-7; 0.89 (3H, d, $J=6.6$ Hz, CHCH_3), 1.04 (3H, d, $J=6.6$ Hz, CHCH_3), 2.50 (1H, dd, $J=10.5$ and 12.5 Hz, NCH_2CH), 3.00 (1H, dd, $J=3.2$ and 12.5 Hz, NCH_2CH), 3.48 (1H, dd, $J=5.9$ and 8.3 Hz, OCH_2CH), 3.95 (1H, dd, $J=7.3$ and 8.3 Hz, OCH_2CH), 4.29 (1H, d, $J=5.9$ Hz, OCH_2N), 4.45 (1H, d, $J=5.9$ Hz, OCH_2N), 4.61 (1H, dd, $J=3.2$ and 10.5 Hz, OCHCH_2). (1*R*,4'*S*)-7; 0.92 (3H, d, $J=6.4$ Hz, CHCH_3), 1.05 (3H, d, $J=6.4$ Hz, CHCH_3), 2.61 (1H, dd, $J=9.5$ and 12.9 Hz, NCH_2CH), 2.90 (1H, dd, $J=3.7$ and 12.9 Hz, NCH_2CH), 3.47 (1H, dd, $J=5.1$ and 8.3 Hz, OCH_2CH), 3.92 (1H, dd, $J=6.8$ and 8.3 Hz, OCH_2CH), 4.28 (1H, d, $J=6.1$ Hz, OCH_2N), 4.31 (1H, d, $J=6.1$ Hz, OCH_2N), 4.66 (1H, dd, $J=3.7$ and 9.5 Hz, OCHCH_2).

Reaction of (*S*)-6 with LiAlH_4 — LiAlH_4 (0.23 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-6 (0.47 g, 2 mmol) in THF (7 ml). The reaction mixture was stirred at -20 — -10°C for 10 h, and worked-up as described above for the reaction of (*S*)-2 to give a mixture of (1*S*,1'*S*)-4 and (1*R*,1'*S*)-4 (0.31 g, 66%). The product ratio was estimated to be 75:25 by the $^1\text{H-NMR}$ spectroscopy, and these compounds were identified by comparison with the diastereomers obtained from (*S*)-2 by LiAlH_4 reduction.

Conversion of (1*S*,4'*S*)-7 into (1*S*,1'*S*)-4—(1*S*,4'*S*)-7 (0.13 g, 0.5 mmol) was reduced with LiAlH_4 (0.08 g, 2 mmol) in THF (3 ml) to give (1*S*,1'*S*)-4 (0.09 g, 69%) by a procedure similar to that used for the reduction of (1*S*,4'*S*)-3 with LiAlH_4 as described above.

Condensation of (*S*)-1 with 2-Phenyloxirane—A suspension of sodium (*S*)-4-isopropyl-1,3-oxazolidin-2-onate (7.5 mmol) in toluene (20 ml), which was prepared as described above, was added dropwise to a refluxing solution of 2-phenyloxirane (2.3 g, 19 mmol) in toluene (12 ml). After being refluxed for 6 h, the reaction mixture was concentrated under reduced pressure and treated with dilute HCl. The whole was extracted with ether, and the organic layer was dried over anhydrous MgSO_4 then concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give a mixture of (1*S*,4'*S*)-3 and (1*R*,4'*S*)-3 (0.29 g, 16%). The amounts of the two isomers were estimated to be nearly equal by $^1\text{H-NMR}$ spectroscopy.

(*S*)-3-1',1'-Diethoxyethyl-4-isopropyl-1,3-oxazolidin-2-one (8)—A solution of (*S*)-1 (16.8 g, 0.13 mol) and NaH (6.3 g, 0.26 mol) in $[(\text{CH}_3)_3\text{N}]_3\text{PO}$ (150 ml) was stirred at room temperature for 9 h. A solution of 2-bromo-1,1-diethoxyethane (28.6 g, 0.15 mol) in $[(\text{CH}_3)_3\text{N}]_3\text{PO}$ (30 ml) was added dropwise to the solution of the sodium salt of (*S*)-1, and the reaction mixture was stirred at room temperature for 8 h. After treatment with a small amount of H_2O , the whole was extracted with ether. The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was distilled *in vacuo* to give (*S*)-8 as a colorless oil, bp 153 — $155^\circ\text{C}/3$ mmHg, (29 g,

90%). IR (CHCl₃): 1750 (C=O) cm⁻¹. MS *m/z*: 246 (M·H⁺). ¹H-NMR (CDCl₃) δ: 0.84 (3H, d, *J*=6.8 Hz, CHCH₃), 0.88 (3H, d, *J*=6.8 Hz, CHCH₃), 1.21 (6H, t, *J*=7.1 Hz, CH₂CH₃), 2.98 (1H, dd, *J*=6.6 and 14.4 Hz, NCH₂CH), 4.64 (1H, dd, *J*=3.9 and 6.6 Hz, O(O)CHCH₂).

Reaction of (*S*)-9 with Phenylmagnesium Bromide—A solution of (*S*)-8 (0.5 g, 2 mmol) in 10% HCl (15 ml) and acetone (5 ml) was stirred at 40–45 °C for 1 h. After removal of the acetone, the whole was extracted with CH₂Cl₂ and the organic layer was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was dissolved in THF (3 ml) and added dropwise to a stirred suspension of phenylmagnesium bromide (4 mmol in 4 ml of THF) under a nitrogen atmosphere. After being stirred at –20––10 °C for 9 h, the reaction mixture was poured into NH₄Cl solution and the whole was extracted with ether. The ethereal solution was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH₂Cl₂ to give a mixture of (1*S*,4'*S*)-3 and (1*R*,4'*S*)-3 (0.33 g, 66%). The amounts of the two isomers were estimated to be nearly equal by ¹H-NMR spectroscopy.

Acknowledgement We are grateful to Mrs. M. Yuyama, Miss T. Tanaka, and Mrs. T. Ogata of Hoshi university for mass spectra, ¹H-NMR spectra, and elemental analysis.

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